

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference 661476		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/JP99/05319	International filing date (day/month/year) 29/09/1999	Priority date (day/month/year) 01/10/1998	
International Patent Classification (IPC) or national classification and IPC C07D235/20			
Applicant BAYER YAKUHIN, LTD. et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

 These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:
 - I ☒ Basis of the report
 - II ☐ Priority
 - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV ☐ Lack of unity of invention
 - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☒ Certain documents cited
 - VII ☒ Certain defects in the international application
 - VIII ☐ Certain observations on the international application

Date of submission of the demand 18/01/2000	Date of completion of this report 20.07.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Bueno Torres, M Telephone No. +49 89 2399 8290 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/JP99/05319

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-120 as originally filed

Claims, No.:

1-10 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 7-10.

because:

- ☒ the said international application, or the said claims Nos. 7-10 relate to the following subject matter which does not require an international preliminary examination (*specify*):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/JP99/05319

see separat sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 1-10
	No: Claims
Inventive step (IS)	Yes: Claims 4
	No: Claims 1-3, 5-10
Industrial applicability (IA)	Yes: Claims 1-6
	No: Claims

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/JP99/05319

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

III. Claims 7-10 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

V. i) The following documents have been taken into consideration:

D1 = Journal of Pharmacology and Experimental Therapeutics, 264(2), 1993, 676-682

D2 = WO-A-95/08540

D3 = US-A-5 693 515

D4 = Nature, 391, 1998, 608-612

ii) Claim 1 of the present application can be considered to be novel vis-à-vis D1 and D4, mainly on account of the fact the substituents R_1 - R_{10} do not represent an amidine moiety (Art. 33(2)PCT).

Claim 1 of the present application can be considered to be novel vis-à-vis D2 and D3 mainly on account of the meaning of the -COA moiety (Art. 33(2)PCT).

iii) The closest prior art is considered to be D1 and/or D4 which also disclose bis-benzimidazolyl derivatives useful as tryptase inhibitors.

D1 states that removal of amidine from one of the benzimidazolyl groups, as in compound 4, leaves an inhibitor 7,1-fold less potent than the most potent congener (see D1, second column on page 677). The relevance of the amidine groups of analogue bis-benzimidazole derivatives in the binding to the enzyme trypsin is also disclosed in D4 (see page 608, last paragraph).

Therefore, in principle having regard for the disclosure of the prior art it is not considered as obvious to eliminate all the amidine groups from the bis-benzimidazolyl derivatives and to replace one amidine group by an amide group.

The problem underlying the invention is therefore considered to be the

provision of further bis-benzimidazolyl derivatives useful as trypsin inhibitors.

In the light of the data given in the description it appears that said problem has been solved by some of the compounds encompassed within the definition of claim 1.

However, the definitions of the moiety A given in claim 1, namely "a non aromatic 5- to 7-membered N-heterocycle which is bound over the nitrogen atom and which optionally contains an oxygen atom or a residue..." and the expressions "5- or 6-membered aromatic or non-aromatic heterocycle..." embrace a high number of possibilities not yet explored by the Applicant. These expressions therefore cover possibilities which are not regarded as obvious modifications of the examples given. Furthermore, they relate to compounds that differ from the tested compounds more than those differ from the compounds of the prior art. It should be borne in mind that only compounds which are suitable for solving the problem underlying the present application can be claimed.

Therefore, claim 1 cannot be reasonably considered to encompass only compounds for which it is inherently likely that all of them or substantially all of them represent a solution to the problem underlying the invention.

At present, in the light of the examples given and of the data available, an inventive step could only be acknowledged for claim 4 (Art. 33(3)PCT).

VI. D5 = WO-A-98/45275

International Filing Date : 01.12.97

International Publication Date : 15.10.98

Priority Data: 07.04.97

D6 = WO-A-99/26932

International Filing Date : 25.11.98

International Publication Date : 03.06.99

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/JP99/05319

Priority Data: 26.11.97 and 17.11.98

For the purposes of this report it has been considered that the priority date of 01.10.98 has been validly claimed. If this were not the case, D5 and D6 could become relevant to assess whether claims 1-10 satisfy the criteria set forth in Art. 33(1)PCT.

It appears that the present subject-matter overlaps with the disclosure of D5 in the case wherein A represents a residue of the formula $-NR_{19}R_{20}$.

- VII. To meet the requirements of Rule 5.1(a)(ii)PCT, the documents D1-D6 should have been identified in the description and the relevant prior art disclosed therein should have been briefly discussed